REMARKS

Claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52 and 57-62 were pending in the present application. By virtue of this response, claims 59, 60 and 62 have been cancelled, claims 27, 33, 39, 45 and 51 have been amended, and new claims 63-73 have been added. Accordingly, claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52, 57-58, 61 and 63-73 are currently under consideration.

Support for the amended and new claims may be found throughout the specification, including the claims, as originally filed and in particular, in at least the following: Example 2 (page 17, line 37); Example 3 (page 29, line 28), Example 12 (referencing sample preparation of Example 2 at page 69, line 26); Example 13 (page 79, line 35; page 80, lines 4-5; page 81, Table 4), Figure 6, Figure 28.

In addition, with regard to the recitation of the intrinsic viscosity of the hyaluronan of molecular weights between 750,000 and 890,000, it is well known to the person skilled in the art that intrinsic viscosity is related to the molecular mass of the polymer (substance) by the Mark-Houwink equation (shown below and also described in Barrow, "*Physical Chemistry*" **1979**; page 764**,** included in the Supplemental Information Disclosure Statement co-filed herewith):

The **Mark–Houwink equation** gives a relation between intrinsic viscosity $[\eta]$ and molecular weight M:

$$[\eta] = KM^a$$

From this equation the molecular weight of a polymer can be determined from data on the intrinsic viscosity and vice versa.

As is appreciated by the skilled artisan, the values of the Mark–Houwink parameters, a and K, depend on the particular polymer and the solvent it is dissolved in. These parameters are

determined for a given polymer/solvent combination by standard techniques well known to the skilled artisan for many decades, such as those described in *"Determination of The Viscosity of Liquids in C.G.S. Units"* Pub.: British Standards Institution, Vol 188; 1957; //en.wikipedia.org/wiki/Mark%E2%80%93Houwink_equation) and the intrinsic viscosity determined by solving this equation is an inherent property of the polymer in the particular solvent.

For a polydisperse polymer such as hyaluronic acid in aqueous solution, the Mark-Houwink equation takes the form:

Intrinsic Viscosity = 0.0000978 x (Molecular Weight$^{0.69}$)

Where the units are meters cubed per kilogram (Note that the Mark-Houwink parameters of $a = 0.0000978$, $K = 0.69$ are empirical constants. These empirical constants vary for differing polymers and solvents. The empirical constants shown are those used by Alchemia).

Solution of the above equation for the molecular weights of 750,000 Da and 890,000 Da, the molecular weights recited in the presently pending claims, yields an intrinsic viscosity for 750,000 Da hyaluronic acid of 11.07dl/gm, and an intrinsic viscosity for 890,000 Da hyaluronic acid of 12.45 dl/gm.

No new matter is believed to have been added by way of these amendments.

Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Applicants expressly reserve the right to pursue presently unclaimed subject matter in one or more continuation and/or divisional applications.

Regarding the Supplemental Information Disclosure Statement (SIDS)

An SIDS is filed herewith. Applicants respectfully request review of the cited references and return of the initialed form SB/08 with the next action. Should the Examiner be unable to

access any of the cited references, she is encouraged to contact the undersigned prior to the issuance of the next action and additional copies will be provided.

Applicants thank the Examiner in advance for her review of the cited references and return of the initialed SB/08s and for her return of earlier SB/08 with the present action.

Request for Examiner Interview

Applicants thank the Examiner in advance for her time and consideration of the amendments and remarks presented herein. Should the amendments and remarks presented herein not fully address the Examiner's concerns, the Examiner is urged to contact the undersigned regarding any outstanding issues prior to the issuance of a further action on the merits.

Regarding the Prior Rejections

Applicants thank the Examiner for her clear indication at page 2 of the Office Action (3rd paragraph) that prior rejections not reiterated in the present action are withdrawn.

Rejections under 35 U.S.C. § 103

A. Claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52, 57, 58 and 61 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over della Valle et al. (US 5,442,053).

While not acquiescing to the Examiner's remarks regarding the alleged obviousness of the previously presented claims, Applicants assert that the presently amended claims are not rendered obvious by della Valle *et al.* Applicants present the amended claims in an effort to further prosecution of the present application.

As an initial matter, the Applicants note that the "Examiner agrees that della Valle does not teach intravenous administration as recited in claims 59 and 60." Applicants note that claims 59, 60 and 62, which each recite intravenous administration or formulation for intravenous administration are not included in the present rejection over della Valle *et al.*

Applicants agree with the Examiner that della Valle *et al.* does not teach or suggest intravenous administration (or formulation for intravenous administration) of compositions of hyaluronan and chemotherapeutic agents as recited in previously pending claims 59-60 and 62. Further, Applicants note that presently pending independent claims 27, 33, 39, 45 and 51, as amended, recite that administration is performed intravenously or that the pharmaceutical compositions are formulated for intravenous administration.

With regard to the Examiner's comments regarding the teaching of della Valle *et al.,* with regard to various molecular weight ranges of hyaluronan at numbered paragraph 6 (bridging pages 3-4) of the present Office Action (shown below), Applicants respectfully assert that della Valle *et al.,* does not render obvious the presently pending claims, which require hyaluronan with "a molecular weight of between 750,000 and 890,000 Da, with an intrinsic viscosity of between 11.07dl/gm and 12.45 dl/gm," as discussed in greater detail below.

6. della Valle does not use hyaluronic acid having molecular weight of 890,000 as recited in generic claims 27, 33, 39 and 51 and dependent claims 30, 36, 42, 48 and 52. However, the disclosure to use hyaluronan having a range of molecular weight or from about 500,000 to about 730,000 Da (claims 5, 8, 18 and 32), and the general teaching that as a vehicle, hyaluronic acid of varying molecular weights can be used (column 18, lines 63-66) and that the molecular weight of HA is generally up to about 8-13 million, suggest that although, molecular weight in the range of about 500,000 to 730,000 Da may be used, hyaluronic acid of other molecular weight may also be used including hyaluronic acid of molecular weight higher than 730,000 Da being mindful of the intrinsic viscosity of the hyaluronic acid carrier vehicle (column 4, lines 13-23). Therefore, taking the general teaching of della Valle, the person of ordinary skill in the art at the time the invention was made would have reasonable expectation of success that using hyaluronic acid having molecular weights in a range that is higher than the 730,000 Da that results in a carrier vehicle having desired viscosity would provide the anticipated therapeutic composition for successful delivery of cytotoxic agents.

As noted above, Applicants note that della Valle *et al.* does not disclose the intravenous administration of hyaluronan (hereafter "HA") with a molecular weight of between 750,000 and 890,000 Da and with an intrinsic viscosity of between 11.07dl/gm and 12.45 dl/gm and chemotherapeutic agents (or intravenous formulations of this combination of HA and chemotherapeutic agents). Instead, as noted by the Examiner and quoted above, della Valle discloses the use of HA of molecular weight 500,000 to 730,000 Da for use in intraocular and intraarticular *injections* and HA of molecular weight of 50,000 to 100,000 for use in wound healing (*topical* application, intradermal *injection*). *See* Abstract, col. 3, lines 12-24 and 48-64, *etc.*)

With regard to the della Valle *et al.*, disclosure of 5-flurouracil (5-FU) and methotrexate in col. 24 as cited by the Examiner, Applicants note that this disclosure, when taken in context with

the paragraph in which they appear, teach that the HA and 5-FU/methotrexate are formulated for *dermatological* applications, not formulated for intravenous, use. *See below:*

> *Examples of active substances to be used alone or in combination or together with other active principles in* ***dermatology*** are: therapeutic agents such as anti-infective, antibiotic, antimicrobial, anti-inflammatory, cytostatic, ***cytotoxic***, antiviral, anesthetic agents, and prophylactic agents, such as sun shields, deodorants, antiseptics and disinfectants. Of the antibiotics the following are of particular note: erythromycin, bacitracin, gentamicin, neomycin, aureomycin, gramicidin and their associations; of the antibacterials and disinfectants: nitrofurazone, mafenids, chlorhexidine, and derivatives of 8-hydroxyquinoline and possibly their salts; of the anti-inflammatory agents: above all the cortocosteroids such as prednisolone, dexamethasone, flumethasone, clobetasol, triamcinolone acetonide, betamethasone or their esters, such as valerianares, benzoates, dipropionates; ***of the cytotoxics: fluorouracil, methotrexate, podophyllin***; and of the anesthetics: dibucaine, lidocaine, and benzocaine. This list is of course only for illustrative purposes and any other agents known or described in literature may be used. Of the examples mentioned for *ophthalmology and dermatology*, it is possible to determine by analogy medicaments according to the present invention which are useful in the above mentioned fields of medicine, such as for example in otorhinolaryngology or odontology or in internal medicine, for example in endocrinology, where it is possible to effect treatments with preparations for intradermic absorption or absorption through the mucous, for example rectal or intranasal absorption, for example such as nasal sprays or inhalations in the oral cavity and in the pharynx. These preparations may, therefore, be for example anti-inflammatory, or vasoconstricting or vasopresors such as those already mentioned for ophthalmology, vitamins, antibiotics, such as those mentioned above, hormes, chemiotherapeutics, antibacterials, etc., these also as mentioned above for use in dermatology. (Col. 24, line 49 through col. 25, line 17. *emphasis added*).

Della Valle *et al.,* does not teach the use of HA of molecular weights greater than 730,000 Da for systemic nor intravenous administration and, in particular does not teach the use of HA of between 750,000 and 890,000 Da and with an intrinsic viscosity of between 11.07dl/gm and 12.45 dl/gm (neither are intravenous formulations with HA of these characteristics taught). For at least the reasons described herein, Applicants also assert that the skilled artisan *would not consider*, as asserted by the Examiner in the last sentence of numbered paragraph 6, page 4 of the present action (*quoted below*), that HA of molecular weights higher than 730,000 Da, and in particular, HA with the characteristics recited in the present claims, appropriate for intravenous use, nor would there be a reasonable expectation by the skilled artisan that use/formulations as recited in the claims would be efficacious and safe for intravenous use.

Therefore, taking the general teaching of della Valle, the person of ordinary skill in the art at the time the invention was made would have reasonable expectation of success that using hyaluronic acid having molecular weights in a range that is higher than the 730,000 Da that results in a carrier vehicle having desired viscosity would provide the anticipated therapeutic composition for successful delivery of cytotoxic agents.

More specifically, della Valle *et al.* describe the isolation and use of two different molecular weight fractions of HA. These fractions are HA of molecular weight 500,000 to 730,000 Da (" HYALECTIN") and HA of molecular weight of 50,000 to 100,000 Da ("HYALASTIN"). The lower molecular weight fraction (50,000 to 100,000 Da) is disclosed as being suitable for use topically in wound healing, while the higher molecular weight fraction (500,000 to 730,000 Da) was identified as suitable for use intraocularly and as a substitute for endobulbar liquids and intraarticularly in therapy in connection with traumatic and degenerative diseases of the joints. *See* col. 3, lines 48-64, *etc.* As noted previously, additional dermatological formulations are also disclosed (*see e.g.,* cols. 24-25).

Della Valle *et al.,* do not teach intravenous use of either the 500,000 to 730,000 Da fraction or the 50,000 to 100,000 Da fraction of HA. Nor do della Valle *et al.* teach the combination of HA molecular weight between 750,000 and 890,000 Da and with an intrinsic viscosity of between 11.07dl/gm and 12.45 dl/gm with anticancer chemotherapeutic agents. Moreover, della Valle would not lead the skilled artisan to predict that intravenous administration of the HA recited in the pending claims would enhance the efficacy of anticancer chemotherapeutics (or the usefulness of compositions formulated for such use) in the treatment of cancer. Thus, Applicants assert that della Valle *et al.,* does not render the pending claims obvious.

In addition, della Valle *et al.* actually teach that *different molecular weight fractions of HA have very different physical (e.g., intrinsic viscosity) and biological properties.* Thus, these *different* molecular weight fractions may (or may not) be useful for *different* indications and these

different molecular weight fractions may (or may not) be utilized by different routes of administration. *See e.g.,* col. 3, line 65 through col. 4, line 31, reproduced below (*emphasis added*).

> The first fraction isolated by the inventors has been named HYALASTINE, and has an average molecular weight of from about 50,000 to about 100,000. This HYALASTINE fraction has been determined to be suitable for therapeutic, veterinary and human use because of its wound healing activity. The second fraction isolated by the inventors has been labelled HYALECTIN, and has an average molecular weight of about 500,000 to about 730,000. This HYALECTIN fraction is suitable for use in ocular surgery as a substitute for endobulbar liquids and for veterinary and human therapy in traumatic and degenerative diseases of the joints.
>
> HYALASTINE can be administered either as an intradermal injection or it can be applied as a topical agent for wound healing. HYALECTIN, on the other hand, is suitable for intraocular and intraarticular injection.
>
> The present inventors have made *intensive studies on the various fractions of HA and, in a significantly more precise way than previously accomplished, have specifically determined the* ***therapeutically useful fractions of HA*** *and the inflammatory and* ***non-useful fractions of HA***. As a result of these studies, the present inventors have identified and investigated two specific characteristics of HA fractions, namely cell mobilization activity and intrinsic viscosity. The wound healing process in animals is facilitated by cellular mobilization, and particularly the mobilization of fibroblasts. On the other hand, cellular mobilization or proliferation activity (i.e., mytosis) is to be avoided in cases of surgery inside the ocular globe. This is particularly true in operations to correct retinal detachment where an increased rate of healing may cause harmful affects.
>
> The i***ntrinsic viscosity*** is also an important parameter to be considered in determining the utility of a fraction of HA. A fraction having a ***high intrinsic viscosity is useful for surgical uses***, in the therapy of diseases of the joints of a traumatic and degenerative nature, and for replacing endobulbar liquids. On the other hand, high viscosity is an ***undesirable*** characteristic for fractions to be utilized as drugs for facilitating wound healing. In fact, fractions to be utilized in wound healing should have low viscosity so as to be more easily used in practical application.
>
> The HYALASTINE fraction identified by the present inventors has been determined to have good mobilization or cell proliferation activity, and low viscosity characteristics. Accordingly, HYALASTINE has the characteristics *desirable* for a material useful in promoting wound healing. The same characteristics make the HYALASTINE fraction *undesirable* for use in intraocular or intraarticular-injection treatments.

Thus, there is no disclosure in della Valle that would allow the skilled artisan to predict the indications for which the particular HA recited in the pending claims would be useful, nor any teaching or suggestion that would predict what route of administration would be suitable. Specifically, there is no basis for predicting that HA of higher molecular weights, *e.g.,* higher than

the 500,000-730,000 Da molecular weight range taught by della Valle to be the *higher* molecular weight fraction of HA with "high *intrinsic* viscosity," would be safe and efficacious for intravenous use (or formulation). In fact, the above-quoted disclosure of della Valle would suggest to the skilled artisan that the particular applications for which a particular molecular weight range of HA is useful is not predictable.

Applicants assert that the skilled artisan, being mindful of the intrinsic viscosity of the higher molecular weight HA as recited in the claims and in view of the teachings of della Valle *et al,* regarding appropriate uses of HA of various weights, as well as appreciating the fact that intrinsic viscosity is an inherent and non-dilutable characteristic of HA would in fact be motivated to *avoid* intravenous use of the HA of molecular weights between 750,000 and 890,000 Da.

For the clarity of the record and to provide additional context, Applicants note that viscosity as a term is often misunderstood. In biological systems there are two different types of viscosity to consider – *solution viscosity* (kinematic or dynamic viscosity) and *intrinsic viscosity*, also known as inherent viscosity or limiting viscosity. Solution viscosity is a measure of the resistance of a fluid to deformation – in everyday terms it is the "thickness" of a fluid. As such it is quite reasonable to conceive that the viscosity of a fluid can be diluted to make the solution less viscous – for example honey can be diluted in water to form a free flowing or "thinner" solution – this is an example of solution viscosity (*see e.g.,* en.wikipedia.org/wiki/Viscosity, provided in the Supplemental Information filed herewith).

On the other hand, intrinsic viscosity (also known as inherent viscosity; *see e.g.* en.wikipedia.org/wiki/ Intrinsic_viscosity, provided in the Supplemental Information filed herewith) is an inherent characteristic of the solute – the dissolved substance *e.g.,* HA (as opposed to the solution) and **cannot be diluted**.

While the intrinsic viscosity may affect the solution viscosity (at a given concentration of solute), the intrinsic viscosity is actually *not* a measure of the solution viscosity itself. Rather,

intrinsic viscosity is a measure of the unit volume of solvent that the solute (HA polymer) would occupy, and is therefore a characteristic of each molecule of a substance.

Alternatively stated, diluting a solution may indeed reduce the *solution* viscosity, but the unit volume of solvent occupied by each molecule of solute (*i.e.,* the intrinsic viscosity) will not (and cannot) change. An analogy would be the swelling of a sponge – the volume occupied by the sponge in water will be constant, regardless of whether the sponge is placed in a bucket of water or a swimming pool of water. As noted previously, intrinsic viscosity is related to the molecular mass of the polymer (substance) by the Mark-Houwink equation.

In referring to the above-quoted passage from della Valle *et al.,* in numbered paragraph 6, page 4, 2nd to last sentence (*emphasis added*), the Examiner states:

> . . . suggest that although, molecular weight in the range of about 500,000 to 730,000 Da may be used, hyaluraonic acid of other molecular weight may also be used including Hyaluronic acid of molecular weight higher than 730,000 Da ***being mindful of the intrinsic viscosity of the Hyaluronic acid carrier vehicle*** (column 4, lines 13-23).

Applicants assert that the skilled artisan, being indeed mindful of the intrinsic viscosity of the higher molecular weight HA as recited in the claims and in view of the teachings regarding appropriate uses of HA of various molecular weights, as well as appreciating the fact that intrinsic viscosity is an inherent property related directly to molecular weight, would not have any expectation of success regarding the efficacy or safety of the HA recited in the pending claims when administered intravenously (or formulated for such administration). With the greatest respect, applicants submit that the sections identified by the Examiner are directed to two different fractions of HA, both of lower molecular weight and therefore having different biological properties than the HA recited in the claims, and must be considered in that context.

Della Valle *et al.,* teach that HA of less than 750,000 Da represents 90% of all HA and that this was previously discarded by Balazs (Column 1 line 66 to column 2 line 6). Della Valle teaches that the material of lower than 750,000 Da previously thought not to be therapeutically useful due to inflammatory activity can in fact be used if further fractionated. Della Vale teaches

that HA of 50,000 to 100,00 Da is useful in drug applications for wound healing. Della Valle *et al.* further teach that HA of 500,000 to 730,000 is *not useful in drug applications due to it's intrinsic viscosity,* but is useful instead in surgical applications for replacing endobulbar fluids (articular uses) and in ocular indications (col. 3, lines 14 to 20). This is further supported by col. 3, lines 60 to 64 where HYLASTIN (50,000 to 100,000 Da HA) can be administered either as an intradermal *injection* or can be applied as a *topical* agent for wound healing. HYALECTIN (500,000 to 730,000 DA HA), on the other hand, is suitable for intraocular or intra-articular *injection*.

In a passage referenced by the Examiner, della Valle *et al.* then specifically and unambiguously state (col. 4, lines 13 to 23, *emphasis added*)

> The ***intrinsic viscosity*** is also an important parameter to be considered in determining the ***utility*** of a fraction of HA. A fraction having a high intrinsic viscosity is useful for surgical uses, in therapy of diseases of the joints of a traumatic or degenerative nature, and for replacing endobulbar liquids. On the other hand, high viscosity (intrinsic) is an undesirable characteristic for fractions to be utilized as drugs for facilitating wound healing. In fact, fractions to be utilized in wound healing should have low viscosity so as to be more easily used in practical application.

As della Valle *et al* identify the fraction of HA of 500,000 to 730,000 Da as a *high* intrinsic viscosity fraction *unsuitable for drug use or wound healing*, the skilled artisan would understand the teaching of della Valle *et al.* to suggest follows that fractions of *even higher* molecular weights of HA (*e.g.,* 750,000 to 890,00 Da as recited in the pending claims), which inherently have a higher intrinsic viscosity, are even *less* desirable for this purpose. Since intrinsic viscosity *cannot* be diluted as discussed above, applicants believe that della Valle, far from rendering the present claims obvious, actually teaches away from the subject matter presently claimed.

Thus, as noted previously, in addition to not disclosing or suggesting combinations of HA of molecular weights between 750,000 and 890,000 Da and anticancer chemotherapeutic agents and their intravenous administration in enhancing the efficacy of these agents in the treatment of cancer, della Valle *et al.* clearly does not lead the skilled artisan to predict the efficacy demonstrated by these formulations and methods, as evidenced by the disclosure of the present

application and, in addition in the September 11, 2006 declaration under 37 CFR §1.132 of Dr. Tracey Brown. Indeed, on considering the teaching of the reference as a whole, the skilled artisan at the priority date of the present application would not predict the surprising enhancement of anticancer chemotherapeutic agent efficacy when combined with the recited HA administered intravenously. Instead, della Valle *et al.* actually teach the skilled artisan the unpredictability of the biological effects of *different molecular weight ranges* of HA and the need to discover the uses and routes of administration for which the various molecular weight fractions are suitable.

Thus, for at least the reasons recited above, Applicants assert that the presently pending independent claims 27, 33, 39 and 45 (and therefore their independent claims) are not obvious in view of della Valle *et al.* In view of the above remarks and amendments, Applicants respectfully request withdrawal of the rejection of claims 27, 33, 39 45, and 51 (and their dependent claims.)

B. Claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52 and 57-62 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Falk *et al.* (US 5,985,850).

While not acquiescing to the Examiner's remarks regarding the alleged anticipation or obviousness of the previously presented claims, Applicants assert that the presently amended claims are neither anticipated nor rendered obvious by Falk *et al.* Applicants present the amended claims in an effort to further prosecution of the present application.

For the clarity of the record, Applicants note that Falk *et al.* does not disclose the intravenous administration of HA of molecular weights between 750,000 and 890,000 Da and chemotherapeutic agents. While the examples of Falk *et al.* are silent as to the molecular weight of HA administered to patients with cancer, the preferred HA taught by Falk *et al.* is characterized as having a molecular weight range of 150,000-225,000 Da, which falls well below the molecular weight of HA recited in the amended claims. *See e.g.,* col. 17, line 33 through col. 18, line 28. An alternative formulation of HA disclosed as "successfully employed" (without supporting data) by Falk *et al.* is the LifeCore™ Biomedical, Inc. HA, characterized by a molecular weight of "<750,000 Daltons." (*See* col. 18, lines 33-58).

The teaching of Falk *et al.* with regard to higher than 730, 000 Da molecular weight HA is made in connection with treatment of the eye (*see* col. 18, line 62 through col. 19, line 25, particularly "f" at lines 14-23) and references US Pat No. 4,141,973 ("Balazs *et al.*"; previously made of record in the SIDS filed August 17, 2009). Balazs *et al.*, which is referenced by Falk *et al.*, teaches the use of HA of greater than 750,000 Da, preferably greater than 1,200,000 Da for ocular (*e.g.,* after intravitreal and other intraocular surgery), intraarticular uses (*e.g.,* supplementation of synovial fluid, after joint surgery, etc.) and topical applications as a barrier to water and microorganisms in skin wounds. *See e.g.,* col. 14, line 8 through col. 15, line 48.

Falk *et al.* does not teach the intravenous use of HA with molecular weights between 750,000 and 890,000 Da HA for the treatment of cancer nor preparation of pharmaceutical formulations of anticancer chemotherapeutic agents and HA formulated for intravenous administration.

Further, there is no teaching or suggestion in Falk *et al.* that would lead the skilled artisan to predict the enhanced efficacy of chemotherapeutic agents when used in combination with the HA recited in the pending claims and administered intravenously. The disclosure of Falk *et al.* describes a wide variety of conditions (*see e.g.,* the table bridging columns 19-20) and chemicals and drugs (*see e.g.,* the table bridging columns 19-20), but without any guidance for the skilled artisan regarding the selection of combinations of HA of particular molecular weights for particular routes of administration or particular indications. The indications in the above-referenced table range from hair growth (indicated to be applied topically) and prevention of topical infections, to treatment of HIV and cancer, but, except for the reference to the Balazs *et al.* teachings described above, provides no teaching of what molecular weight HA is suitable for effective treatment of a given indications, other than teaching that HA of molecular weight 150,000-225,000 Da is the preferred HA disclosed, with HA of molecular weight less than 750,000 as a possible alternative.

There is nothing in Falk *et al.* to lead a skilled artisan to predict the enhanced efficacy of intravenously administered HA of molecular weights between 750,000 and 890,000 Da when combined with anticancer chemotherapeutics for the treatment of cancer, such as is demonstrated in

the present application (*see e.g.,* Example 2 and Figure 7-9). Further evidence of the superiority of HA of molecular weights greater than even the alternative HA described by Falk *et al.* (which is less than 750,000 Da), is provided by the declaration of Dr. Tracey Brown under 37 CFT 1.132 and filed with the Office September 11, 2006 (*see e.g.,* Figure 1 (a &b) through Figure 3).

Additionally, in rejecting the claims in light of Falk, the Examiner argues, *e.g.,* as quoted below, that Falk contemplates higher molecular weight HA's (column 18 lines 64-65) and provides directions for the use of the higher molecular weight HA by dilution the HA so as to ensure no intra-muscular coagulation (column 19 lines 32-34).

> However, Falk contemplates the use of HA having higher molecular weight and the requirement is that the composition be diluted to permit administration that does not coagulate (column 19, lines 32-34) and specifically HA having molecular weight in the range of 750,000 to 1,200,000 is suggested (column 18, lines 64, 65). Therefore, taking the general teaching suggestion of Falk, the person of ordinary skill in the art at the time the invention was made would have reasonable expectation of success that using hyaluronic acid having molecular weights in a range of 750,000 to 1,200,000 and using the appropriate dilution to provide a composition having a viscosity such that the composition does not coagulate, would be suitable carrier vehicle having desired viscosity that would provide the anticipated therapeutic composition for successful systemic delivery of cytotoxic agents.
>
> (page 6, present Office Action)

With respect, the directions of Falk to simply dilute the solution to ensure no intramuscular coagulation are scientifically not on point. As discussed above, intrinsic viscosity is not a dilutable characteristic of any HA or any other polymer. The principle that intrinsic (limiting) viscosity cannot be diluted was well understood by those skilled in the art at the time of Falk and in fact Falk references Balazs (US 4,141,973) and Balazs provides a discussion of both limiting viscosity (column 5 lines 15 to 35) and kinematic viscosity (column 6 lines 3 to 14). While Falk

may direct the addressee to dilute material for intramuscular injection, such a dilution can only overcome the kinematic viscosity of the solution thereby making delivery less painful – dilution cannot overcome the high intrinsic viscosity which Balazs and Della Valle have taught as an undesirable characteristic for drug usage.

Intramuscular coagulation results from precipitation of the injected substance in the muscle and requires the substance is injected into the muscle. It is well established that the largest practical intramuscular injection is up to 3 mL (Stedmans Medical Dictionary 5th Ed page 766-767). The current application requires intravenous infusion NOT intramuscular injection. The volumes infused are typically greater than 250 mL and often up to 1 litre – far beyond the ambit of an intramuscular injection.

As noted above in the remarks pertaining to della Valle *et al.*, the skilled artisan would have be well aware of these facts and would not be persuaded by the teaching in Falk referenced by the Examiner to *intravenously* administer HA of molecular weights of between 750,000 and 890,000 Da. Thus to the skilled artisan, Falk quite clearly contemplates a different mode of administration for higher molecular weight/higher *intrinsic* viscosity HA formulations. For at least the reasons described herein, Applicants assert that Falk would not direct the skilled artisan to attempt intravenous infusion of high intrinsic viscosity HA formulations with any expectation of success with regard to efficacy and/or safety and does not render the pending claims, as amended, obvious.

In view of the above remarks and amendments, Applicants respectfully request withdrawal of the above rejections under 35 U.S.C. §103(a).

Declaration by Dr. Tracy Brown

The declaration under 35 U.S.C. §1.132 of Dr. Tracey Brown of August 19, 2008 was regarded by the Examiner as insufficient to overcome the rejection of claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52 and 57-62 based upon the rejection under 35 U.S.C. 103(a) as obvious over Falk et al. (US 5,985,850).

While not agreeing with the comments set forth in the Office Action regarding the alleged insufficiency of this declaration, Applicants note for the Examiner's convenience that the declaration under 35 U.S.C. §1.132 of Dr. Tracey Brown referred to in the above remarks is the declaration of Dr. Tracey Brown previously submitted to the Office and with OIPE stamp date of September 11, 2006.

Applicants further note for the Examiner's convenience that the data presented in this declaration provides experimental results for HA formulations of molecular weights (750,000 Da and 880,000 Da) falling within the claimed HA molecular weight range and also specify the concentration ("low:" 3.3 μg/ml; "high:" 86 μg/ml) of HA used in the experiments. Further, various concentrations of 5-FU and methotrexate were used in the experiments and the concentrations (nM) are specified in the data presented.

Additionally *in vivo* experimental data demonstrating the efficacy methods and formulations presently claimed were also presented in the 35 U.S.C. §1.132 of Dr. Tracey Brown previously submitted to the Office and with OIPE stamp date of October 28, 2005. *See e.g.,* Figure 3, 824,000 Da HA (13.3 mg/kg) with 50 mg/kg of irinotecan.

CONCLUSION

In view of the above, each of the presently pending claims in this application are believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **229752005700**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 16, 2010

Respectfully submitted,

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